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Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis

A meta-analysis

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Abstract

Objective: Compelling evidence has shown that aggressive resuscitation bundles are one of the cornerstones of the successful treatment of patients with sepsis. Recent studies suggest that lactate normalization during resuscitation is a more powerful indicator of resuscitative adequacy; however, early lactate clearance-guided therapy is still not recommended. We performed this meta-analysis to evaluate the effect of early lactate clearance-directed therapy as a potentially more effective resuscitation target.

Methods: Studies were identified using PubMed, Embase, and the Cochrane Library without region, publication type, or language restrictions. Randomized trials were included when they compared the efficacy and safety of lactate clearance-guided resuscitation versus central venous oxygen saturation ($ScvO_2$)-guided therapy. The primary outcome was mortality, and the secondary outcomes were intensive care unit (ICU) stay, length of hospital stay, mechanical ventilation time, Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score, and Sepsis-related Organ Failure Assessment (SOFA) score.

Results: Seven randomized controlled trials encompassing 1301 cases were reviewed. Compared with guided $ScvO_2$ therapy, early lactate clearance-directed therapy was associated with decreased in-hospital mortality (relative ratio [RR] 0.68, 95% confidence interval [CI] 0.56 to 0.82), shorter ICU stay (mean difference [MD] −1.64 days, 95% CI −3.23 to −0.05), shorter mechanical ventilation time (MD −10.22 hours, 95% CI −15.94 to −4.5), and lower APACHE-II scores (MD −4.47, 95% CI −7.25 to −1.69). However, patients undergoing early lactate clearance-guided therapy had similar lengths of hospital stay and similar SOFA scores.

Conclusions: As a specific indicator of resuscitation outcome, lactate clearance alone is superior to $ScvO_2$ alone during a standard resuscitation paradigm. The optimal or desired rate of lactate clearance is still a contentious area. To guide resuscitation and normalize lactate levels in patients, repeating lactate measurements every 2 hours until the patient has met a lactate clearance of 10% or greater may be helpful.

Trial registration number: PROSPERO CRD42018100515.

Abbreviations: APACHE-II = Acute Physiology and Chronic Health Evaluation-II, CI = confidence interval, df = degrees of freedom, ED = emergency department, EGDT = early goal-directed therapy, ICU = intensive care unit, MD = mean difference, RCT = randomized controlled trials, RR = relative ratio, $ScvO_2$ = central venous oxygen saturation, SOFA = Sepsis-related Organ Failure Assessment, SSC = Surviving Sepsis Campaign, TSA = trial sequential analysis.

Keywords: early lactate clearance-directed therapy, meta-analysis, $ScvO_2$-guided therapy, sepsis

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1. Introduction

Sepsis, which can cause life-threatening organ dysfunction, contributes to 33% to 50% of inpatient hospital deaths.[1–3] Serum lactic acid levels have long been a diagnostic indicator for global tissue hypoxia and serve to identify patients with sepsis.[4,5] In recent years, the prognostic value of lactic acid was been further recognized, as increased initial lactate levels have been associated with mortality among all-comers with sepsis[6,7]; moreover, early lactate clearance in sepsis patients is associated with improved survival.[8]

The Surviving Sepsis Campaign (SSC) international consensus guidelines recommend an hour-1 bundle that remeasures lactate level for patients with septic shock.[9] Furthermore, the SSC created a research committee for the purpose of developing a list of research priorities related to sepsis. Of these, the top 2 clinical priorities included the following questions[10]: Can targeted medicine approaches determine which therapies will work for which patients at which times? What are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated? To ensure that the effect of early lactate clearance-directed therapy is meaningful, it is important to understand

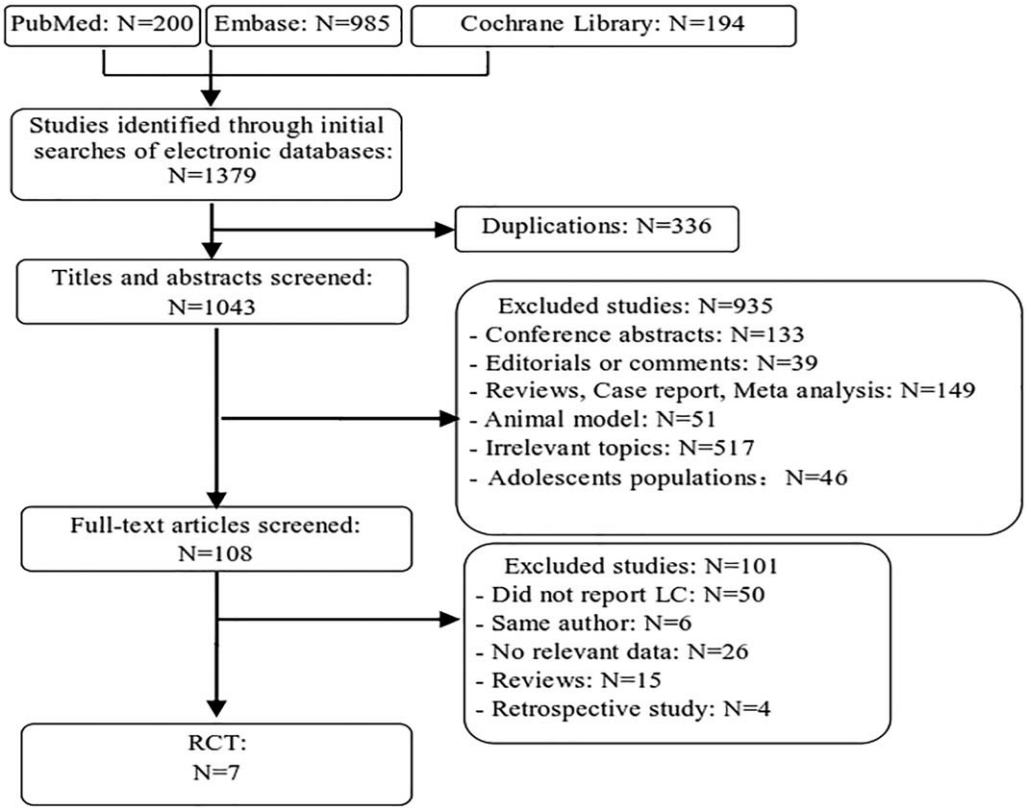


Figure 1. Flow diagram of study inclusion. RCT = randomized controlled trial.

when lactate level should be remeasured, and what the target of optimal lactate clearance should be.

The SSC has recommended an aggressive resuscitation strategy of early goal-directed therapy (EGDT) involving central venous oxygen saturation ($ScvO_2$)-guided therapy, which is used to evaluate tissue perfusion to balance oxygen delivery and metabolic demands.[11] However, the results of the ProCESS, ARISE, and ProMISe trials created doubt as to whether $ScvO_2$ is relatively useful. A meta-analysis of their findings (PRISM study) used the first and second steps in the EGDT as the routine

Table 1

Characteristics of included randomized controlled trials included in the meta-analysis.

	Number: total (LC/control)	Goals in LC	Goals in control group	Follow-up	Risk of bias
Jones et al 2010[16]	300 (150/150)	LC > 10%/6 h UP > 0.5 mL/kg/h MAP > 65 mmHg	$ScvO_2$ > 70% UP > 0.5 mL/kg/h MAP > 65 mmHg	In-hospital mortality	Low
Puskarich et al, 2012[17]	353 (178/175)	LC > 10%/6 h	$ScvO_2$ > 70%,	In-hospital mortality	Low
Zhou et al, 2017[15]	360 (180/180)	LC>30%/6h CVP > 8 mmHg MAP > 65 mmHg	$ScvO_2$ > 70% CVP > 8 mmHg MAP > 65 mmHg	60-Day mortality	Low
Tian et al, 2012[19]	62 (43/19)	LC > 10%/6 h OR LC > 30%/6 h UP > 0.5 mL/kg/h MAP > 65 mmHg	$ScvO_2$ > 70%, UP > 0.5 mL/kg/h. MAP > 65 mmHg	28-Day mortality	Low
Wang et al, 2014[8]	57 (26/31)	LC > 50%/6 h UP > 0.5 mL/kg/h. MAP > 65 mmHg	$ScvO_2$ > 70% UP > 0.5 mL/kg/h MAP > 65 mmHg	28-Day mortality	Low
Lyu et al, 2015[20]	100 (50/50)	LC > 10%/6 h UP > 0.5 mL/kg/h MAP > 65 mmHg	$ScvO_2$ > 70% UP > 0.5 mL/kg/h MAP > 65 mmHg	28-Day mortality	Low
Yu et al, 2013[18]	50 (25/25)	LC > 10%/6 h UP > 0.5 mL/kg/h MAP > 65 mmHg	$ScvO_2$ > 70% UP > 0.5 mL/kg/h MAP > 65 mmHg	28-Day mortality	Low

LC = lactate clearance, MAP = mean arterial pressure, $ScvO_2$ = central venous oxygen saturation, UP = urine output.

treatment for all treatment groups before randomization, so that $ScvO_2$ and central venous pressure had reached the normal level before randomization.[12]

More recently, many studies have investigated the role of lactate clearance in predicting patient outcomes, but the results are conflicting. To better define the accuracy of lactate clearance in improving mortality in sepsis patients, we performed this meta-analysis with the hypothesis that lactate clearance-guided therapy decreases mortality to a greater extent than other therapies. Although the role of central line placement and the use of $ScvO_2$ in the emergency department (ED) have evolved since many of the included studies were performed, better understanding the role of lactate clearance as a superior resuscitation endpoint remains important.

2. Methods

A prospective study protocol comprising objectives, literature search strategies, inclusion and exclusion criteria, outcome measurements, and methods of statistical analysis was prepared a priori according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis.[13,14]

2.1. Ethical review

Personal medical data were not involved in this study, as this is a study based on secondary analysis of literature. Ethical approval was not necessary.

2.2. Search strategy

Database searches of articles published between October 1, 1976 and February 6, 2018 were conducted using PubMed, Embase, and the Cochrane Library. The search strategy was as follows: ("lactate clearance," or "lactate normalization," or "lactate kinetics," or "lactate cut-off," or "lactate reduction") AND ("sepsis," or "severe sepsis," or "septic shock") AND (title or abstract). The related articles function was used to broaden the search results.

2.3. Study eligibility criteria

We included randomized controlled trials (RCTs) that fulfilled the following criteria: adults with sepsis, severe sepsis, or septic shock; studies comparing combined lactate clearance-guided therapy with $ScvO_2$-guided therapy; sufficient data available to calculate an relative ratio (RR) or mean difference (MD) with the 95% confidence interval (95% CI); and outcome measures that included mortality incidences. Studies that did not meet these 4 criteria were excluded.

2.4. Study selection

Two authors screened titles and abstracts independently to identify and exclude duplicate manuscripts and those that did not meet the inclusion criteria. The full texts of articles in which the titles and abstracts appeared to meet the inclusion criteria were reviewed to determine their eligibility. When multiple reports describing the same population were published, the most recent or most complete report was used. Any disagreement was resolved by discussion with the senior authors.

2.5. Data abstraction and quality assessment

The following data were extracted from eligible studies: first author name, year of publication, study design, study sample size, study population characteristics, goals for the lactate clearance-directed and control groups, and the reported outcomes. The date of extraction was entered into a pregenerated standardized Excel file. The primary endpoint was the in-hospital mortality rate. The secondary endpoints were hospital length of stay, intensive care unit (ICU) length of stay, time on mechanical ventilation, Sequential Organ Failure Assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE-II) score.

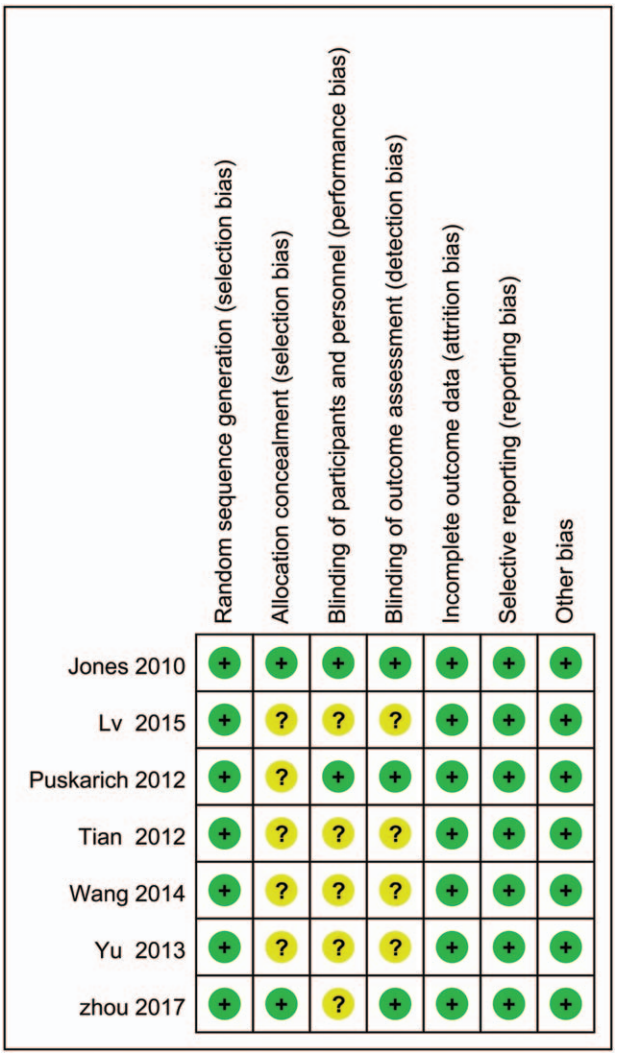
The methodological quality of each RCT was assessed using the Cochrane risk of bias tool. Two authors rated each study according to seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Where discrepancies arose, articles were re-examined and consensus was reached by discussion with senior authors.

2.6. Statistical analysis

The RRs with 95% CIs were determined following the statistical analysis of dichotomous variables, whereas the MDs with 95%

Table 2

Risk of bias summary.



CIs were calculated for continuous variables. Statistical algorithms were used to calculate standard deviations for continuous data, along with their means and range values. Heterogeneity between studies was assessed using the χ^2 and I^2 statistic; higher χ^2 and I^2 values indicated greater heterogeneity between studies. The assumption of homogeneity between the groups was deemed invalid if the P value was <.1, and the random-effects model was used after exploring the causes of heterogeneity. Otherwise, the fixed-effects model was used. Begg test and funnel plot analyses were used to determine the presence of publication bias. Sensitivity analyses were performed for all studies. Trial sequential analysis (TSA) was performed to estimate the optimal sample size for the plausible effects of lactate clearance-guided therapy on sepsis. All meta-analyses were performed using Review Manager 5.3 and STATA SE 12 (Cochrane Collaboration, Oxford, UK).

3. Results

We recovered 1379 records in our initial search. After omitting duplicates and screening the titles and abstracts, 108 articles were deemed to be potentially eligible for inclusion. After screening the full texts of these articles, 7 RCTs[8,15–20] describing studies of 1301 patients that compared lactate clearance-directed therapy to $ScvO_2$-guided therapy were ultimately included in the meta-analysis. The study selection flowchart is shown in Figure 1. All trials, populations, interventions, comparisons, follow-up, and risk of bias are described in Table 1; there was a low risk of bias in the characteristics of the included studies.

The qualities of the included studies were generally high (Table 2). True randomization was employed in all 7 RCTs. Three studies adopted an appropriate protocol for treatment assignment and provided information about allocation concealment or the blinding method.[15–17] Matching criteria between the groups were unavailable, although 7 studies mentioned the length of follow-up. Methods for handling missing data and intention-to-treat analyses were adequately described in 3 studies.[15–17]

3.1. Primary outcomes

All 7 trials compared the effects of lactate clearance-guided therapy versus $ScvO_2$-guided therapy on in-hospital mortality; the former was found to produce significantly better in-hospital survival rates (RR 0.68, 95% CI 0.56 to 0.82; $P<.00001$; fixed-effect model) (Fig. 2) with no significant heterogeneity between studies ($\chi^2=2.87$, degrees of freedom [df]=7, $P=.90$, $I^2=0\%$). All 7 RCTs were included in a sensitivity analysis, the results of which did not change the significance of the outcomes regarding in-hospital mortality rates (Table 3).

3.2. Secondary outcomes

Hospital length of stay, for which data were available for 350 patients across 2 studies, was shorter in the lactate clearance-guided therapy group than in the $ScvO_2$-guided therapy group; however, the difference was not statistically significant (MD −1.24, 95% CI −3.66 to 1.19, $P=.32$; fixed-effect model) (Fig. 3A), with no significant inter-study heterogeneity ($\chi^2=1.67$, df=1, $P=.20$, $I^2=40\%$).

Six of the studies that, encompassing 948 patients, showed a significantly shorter ICU length of stay in the lactate clearance-

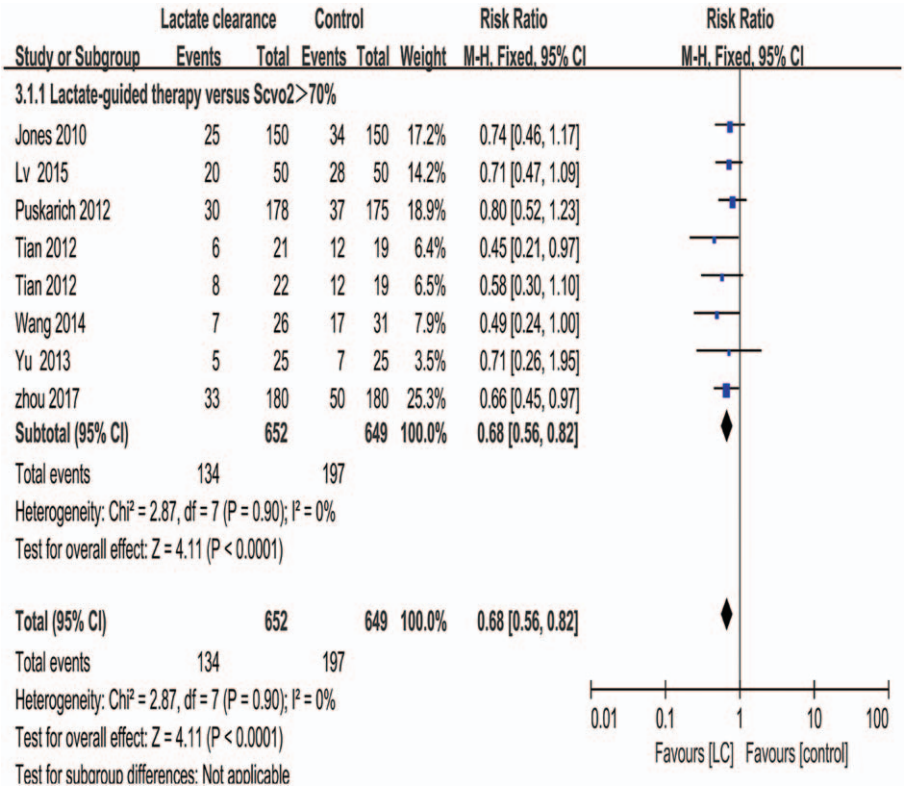


Figure 2. Effect of lactate clearance-guided therapy on in-hospital mortality compared with $ScvO_2$-guided therapy. CI=confidence interval, M-H=Mantel-Haenszel.

Table 3

Sensitivity analysis of in hospital mortality.

Study omitted	Estimate	[95% Confidence interval]	
Zhou et al, 2017[15]	0.6719238	0.54323834	0.83109304
Puskarich et al, 2012[17]	0.64835759	0.52749046	0.79691975
Jones et al. 2010[16]	0.65518259	0.53448589	0.80313481
Tian et al, 2012[19]	0.68360884	0.56381558	0.82885444
Lyu et al, 2015[20]	0.66145875	0.5380522	0.81316957
Wang et al, 2014[8]	0.68401598	0.563602	0.8301565
Yu et al, 2013[18]	0.66725748	0.55182676	0.80683391
Tian et al, 2012[19]	0.67538727	0.5561682	0.82016188
Combined	0.66891748	0.55502693	0.80617816

directed therapy group (MD −1.64 days, 95% CI −3.23 to −0.05; $P=.04$; random-effects model) (Fig. 3B), with significant inter-study heterogeneity ($\chi^2=19.91$, df=6, $P=.003$; $I^2=70\%$).

Data on the duration of mechanical ventilation were available in 4 studies covering 598 patients. Patients receiving lactate clearance-directed therapy had significantly shorter mechanical ventilation durations (MD −10.22 days, 95% CI −15.94 to −4.5; $P=.0005$, fixed-effect model) (Fig. 4A), with no significant inter-study heterogeneity ($\chi^2=4.54$, df=4, $P=.34$, $I^2=12\%$).

Data on SOFA scores, which were extracted from 2 studies that assessed a total of 357 patients, showed no significant difference between the 2 groups (MD −0.11, 95% CI −0.91 to 0.69; $P=.79$, random-effects model) (Fig. 4B); significant inter-study heterogeneity was observed ($\chi^2=0.69$, df=1, $P=.41$; $I^2=0\%$); however, these results were deemed unreliable by a sensitivity analysis.

APACHE-II scores, which were evaluated in 2 of the studies, were significantly improved in the lactate clearance-directed therapy group (MD −4.47, 95% CI −7.25 to −1.69; $P=.002$, random-effect model) (Fig. 4C), with no significant inter-study heterogeneity ($\chi^2=0.00$, df=1, $P=.96$, $I^2=0\%$).

Figure 5 shows a funnel plot of the studies included in this meta-analysis that reported in-hospital mortality rates. All rates lie inside the 95% CIs with an even distribution around the vertical line, indicating no obvious publication bias.

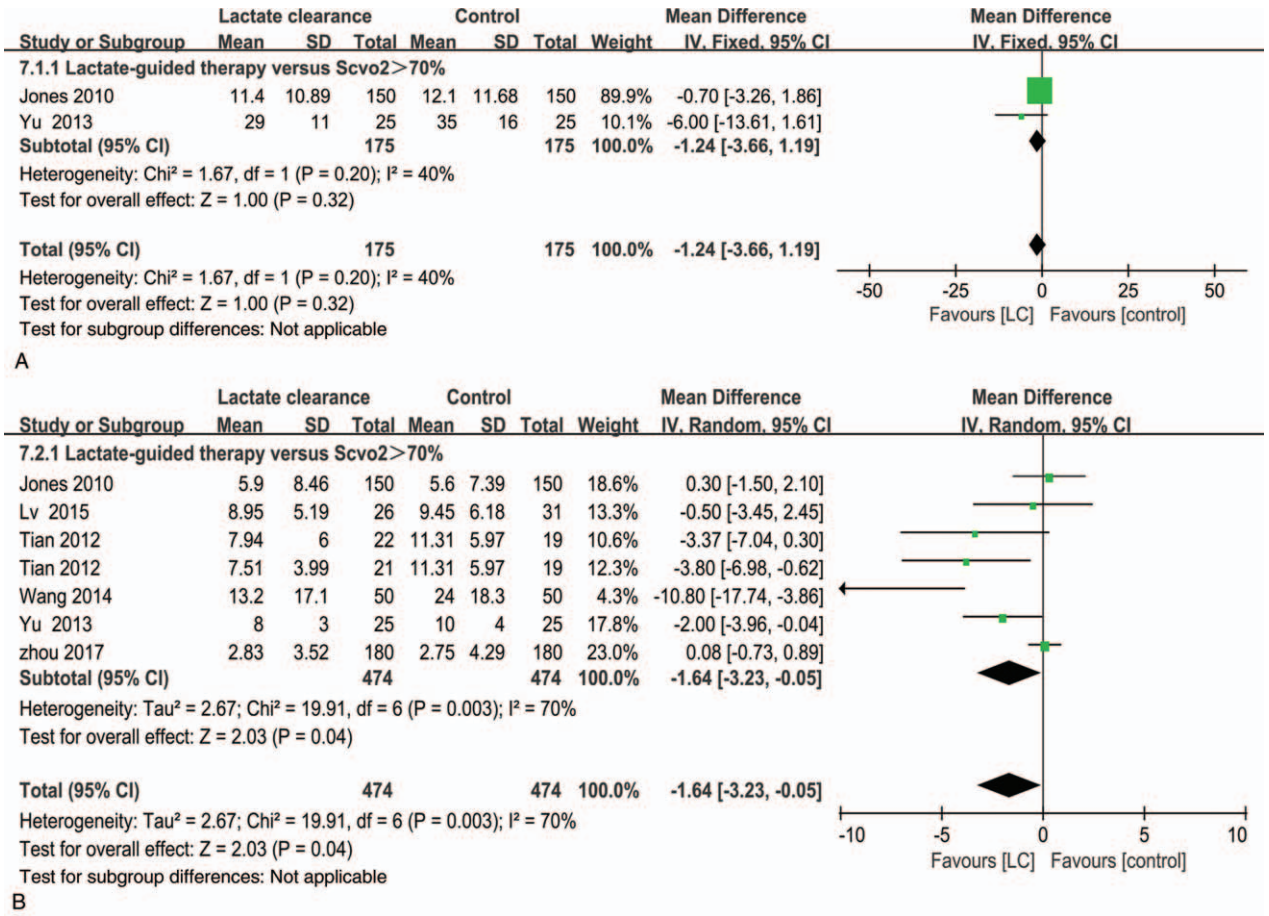


Figure 3. Effect of lactate clearance-guided therapy on hospital length of stay (A) and intensive care unit length of stay (B) compared with early goal-directed therapy. CI = confidence interval, SD = standard deviation.

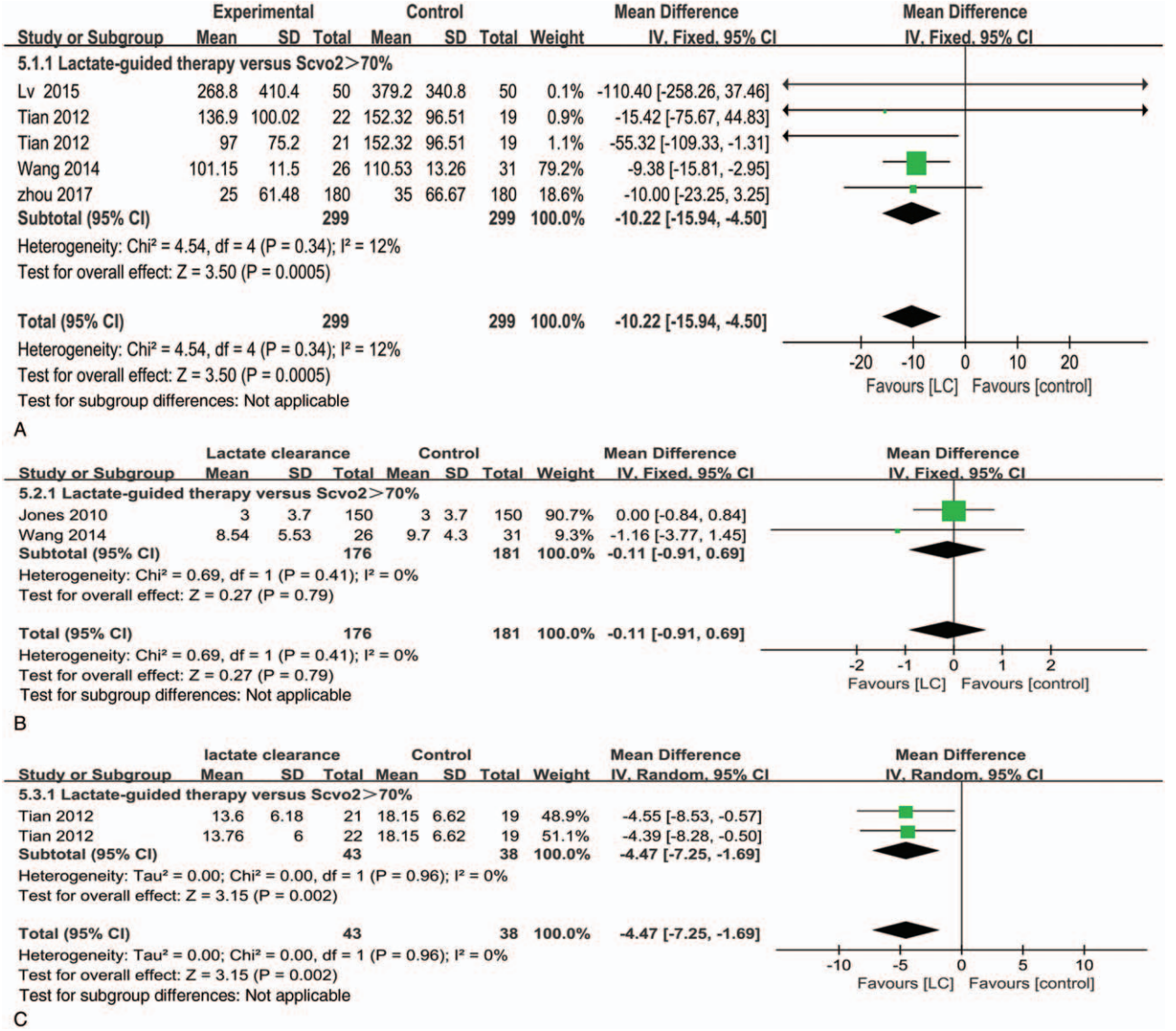


Figure 4. Effect of lactate clearance-guided therapy on mechanical ventilation (A), Sepsis-related Organ Failure Assessment score (B), Acute Physiology and Chronic Health Evaluation-II (C) compared with early goal-directed therapy. CI = confidence interval, SD = standard deviation.

TSA was performed to determine the optimal information size using standard software TSA version 0.9 Beta. The results showed 80% power, an alpha error of 0.05, a beta error of 0.20, a control event proportion obtained from the results of the meta-analysis, and a relative risk reduction of 20% in all-cause mortality. The TSA results are shown in Figure 6: the cumulative *z* value passed the traditional boundary value and TSA boundary value, when the sixth study was included. The conclusion is confirmed in advance, no more experimental proof is needed, although it does not reach the required information size (2693).

4. Discussion

Although the SSC guidelines provide multiple recommendations on the treatment of sepsis, significant knowledge gaps remain. The top research priorities include identifying endpoints for volume resuscitation as well as volume resuscitation titration methods.[10] We conducted this investigation of 7 RCTs to identify a better target resuscitation endpoint, and evaluated the benefits of early lactate clearance-directed therapy for sepsis. Early lactate clearance-directed therapy was associated with decreased mortality. Other endpoints were also improved compared to $ScvO_2$-guided therapy. Thus, lactate clearance appears to be superior to $ScvO_2$ during standard resuscitation efforts. To guide resuscitation and normalize lactate levels in patients, repeating lactate measurements every 2 hours until the patient has met a lactate clearance of ≥10% may be helpful

The present study may be the largest to date to compare lactate clearance alone to $ScvO_2$ alone and to indicate the optimal time for remeasuring lactate level and the target of optimal lactate clearance. Our pooled analysis may be considered more reliable than 2 previous meta-analyses that compared lactate clearance-directed therapy to other methods using 4 and 5 RCTs, respectively.[21,22] Gu et al[21] published a letter in *Intensive Care Medicine* that compared lactated clearance guided therapy with usual care which included RCTs published before 2013. Lu et al[22] published a meta-analysis in 2018 that included RCTs published before 2014. Moreover, the results of the TSA

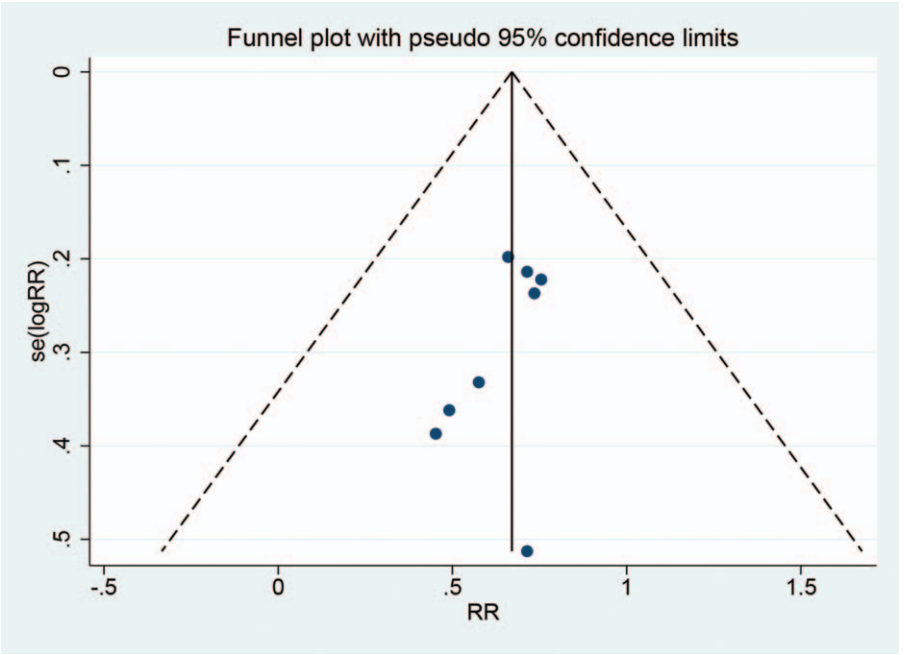


Figure 5. Publication bias of in-hospital mortality. RR = relative ratio

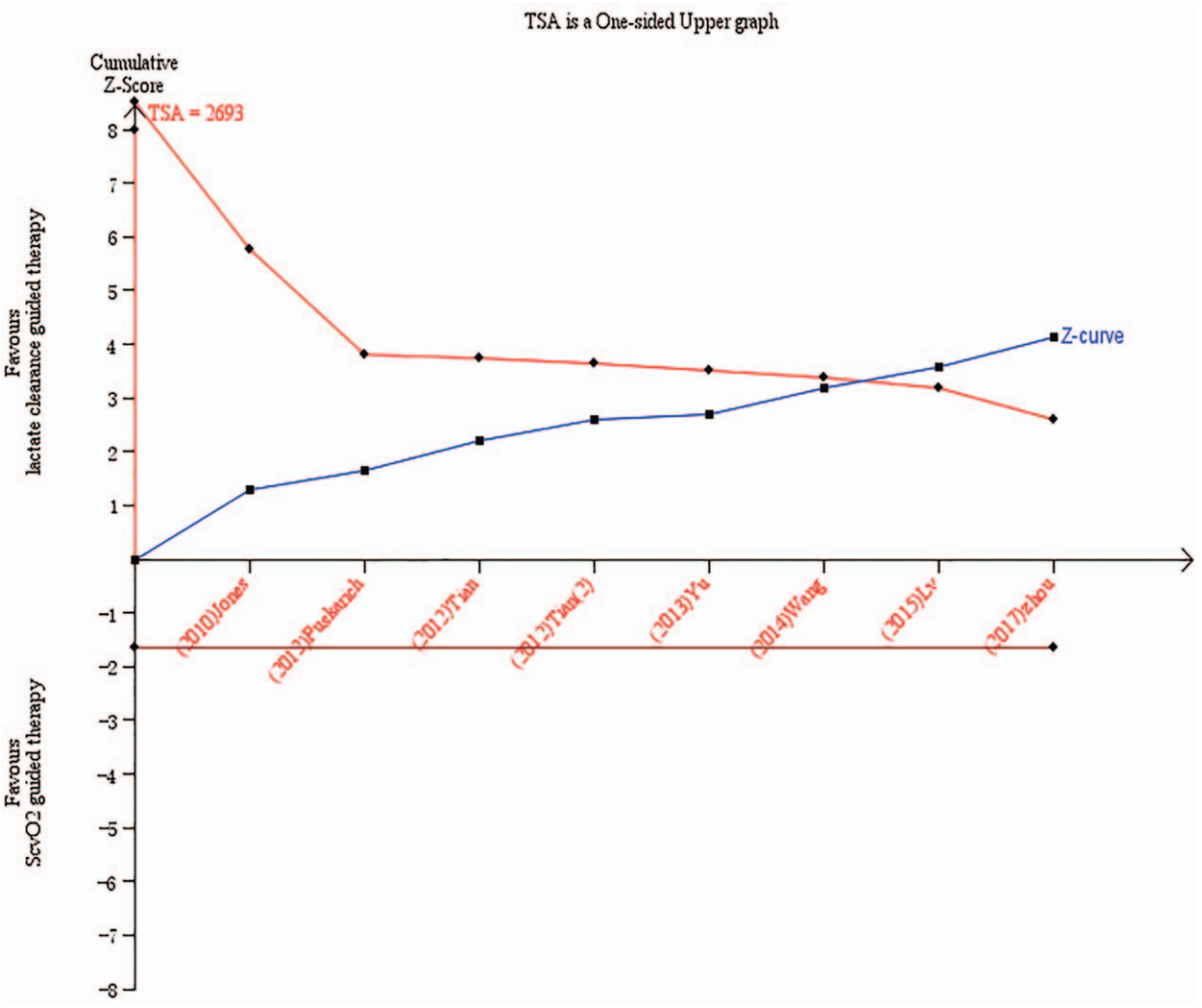


Figure 6. Trial sequential analysis. $ScvO_2$ = central venous oxygen saturation, TSA = trial sequential analysis

performed in our study indicate that our findings are conclusive, which was not determined in the 2 previous meta-analysis. The potential application of our results also appears reasonable given that lactate is a better indicator of total body homeostasis than oxygen-derived factors; it is widely accepted that elevated blood lactate can reflect anaerobic metabolism caused by tissue hypoxia in critically ill patients.[23] Lactate clearance can be used to assess the oxygen supply of microcirculation, as it reflects the cellular aerobic metabolism and oxygen uptake statuses. Hence, combined lactate clearance may be a more reliable guide for fluid resuscitation in patients with sepsis.

The secondary endpoints of the present study showed that lactate clearance was associated with a shorter ICU length, shorter mechanical ventilation time, and lower SOFA score than $ScvO_2$-guided therapy. Lactate clearance at a discrete time point appears to be a reliable indicator of the severity of sepsis and of prognosis. This benefit is consistent with previous findings that a lower lactate clearance rate indicates a high risk of mortality and organ dysfunction,[24] and that lactate clearance may be used as a measure of improvement in the severity of abdominal septic shock.[25] Lactate clearance is an important measure when monitoring and managing patients with severe sepsis and septic shock.[26] Preventing possible hypoperfusion injury to important tissues and organs owing to falling blood pressure, starting early fluid recovery when important tissues and organs appear to be lowly perfused, and preventing further deterioration of organ ischemia-hypoxia may help achieve recovery as soon as possible and maximize the chances of a good prognosis. Lactate significantly increases during tissue perfusion, and its rise can be detected earlier than changes in hemodynamic markers.

Finding ideal endpoints of volume resuscitation has become a hot topic of discussion. In recent years, some scholars have proposed that the increase of central venous-to-arterial carbon dioxide tension difference (Pcv-aCO2) can be an indicator of tissue hypoperfusion to guide liquid recovery.[27] P (v-a)CO2/C (a-v)O2-directed resuscitation did not improve prognosis compared with $ScvO_2$ in severe sepsis and septic shock.[28] However, whether it is superior to lactate clearance-guided therapy oriented therapy is still a lack of relevant research. More RCTS are needed to compare the effects of different fluid resuscitation means on the prognosis of sepsis.

This meta-analysis had a few limitations. First, most of the included articles did not completely meet our standards, and some were of low quality. Furthermore, some positive results of lactate-directed therapy were not reliable according to sensitivity analyses. Therefore, further research on determining the optimal lactate clearance parameters for use during resuscitation is needed. Second, the studies included in the analysis were performed in ICUs and emergency departments; therefore, the included patients may not reflect populations in other hospital wards. Third, our study showed a correlation between lactate clearance and short-term patient survival but did not assess long-term survival rates and economic costs. Finally, this meta-analysis did not address or incorporate individual factors at the patient level.

5. Conclusions

Early lactate clearance-guided therapy was found to be more effective than $ScvO_2$-oriented therapy in terms of significantly reducing mortality, shortening the length of ICU stay and length of mechanical ventilation, and reducing APACHE-II scores. We found no significant differences in length of hospital stay or SOFA scores. Compared to with $ScvO_2$-guided therapy even after sensitivity analysis, the early lactate clearance-guided therapy showed sustained significant improvements in in-hospital mortality rate, and there were no obvious publication biases. Although the benefits of early lactate clearance-guided therapy may be primarily attributed to treatments administered within the first 6 hours, the underlying mechanisms by which lactate clearance-guided therapy benefits these patients are yet to be determined.

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Writing – original draft: JianZhen Pan, MiLin Peng, Xia Hu, AiMin Wang.
Writing – review & editing: JianZhen Pan, MiLin Peng, Xia Hu, AiMin Wang.

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